REMARKS

In paragraph 3, on page 2 of the Office Action, the Examiner again rejects Claim 41 (and new Claim 47) under 35 U.S.C. § 112, first paragraph.

Specifically, the Examiner states that the Bycroft and Molnar-Kimber Declarations establish that one skilled in the art would not previously have expected that monoclonal antibodies to rapamycin could be prepared. The Examiner contends that this expectation is relevant to both obviousness and enablement issues.

The Examiner contends that given that it would have been unexpected that monoclonal antibodies to rapamycin could be prepared, it is unclear how one skilled in the art could prepare such antibodies. The Examiner contends that, in the present specification, Applicants have provided an enabling and written description of the preparation of antibodies using specific immunogens, and thus apparently contends that the claims must be limited to these immunogens.

For the following reasons, Applicants respectfully traverse the Examiner's objection.

Applicants note that the Examiner has failed to cite any legal precedent in support of her position.

Indeed, Applicants respectfully submit that the Examiner has confused the standard for enablement with the standard for obviousness. The standard for enablement is whether it would require "undue experimentation" to practice the scope of the invention as claimed, whereas the standard for obviousness is

whether, in light of the prior art, there was a "reasonable expectation of success".

The Bycroft and Molnar-Kimber Declarations were submitted to rebut the Examiner's obviousness rejection, not an enablement rejection. Further, contrary to the Examiner's apparent contention, the Bycroft and Molnar-Kimber Declarations do not focus on the specific immunogen employed in order to overcome the prior art rejection. That is, contrary to the Examiner's contention, Applicants' invention does not lie in determining which specific rapamycin-carrier conjugate will provide rapamycin specific antibodies. Rather, as discussed therein, and in the Amendment filed February 7, 2002, Applicants' invention lies in the discovery that one could successfully make antibodies specific to rapamycins at all.

In particular, the present invention is unobvious over the prior art, since at the time of the present invention, in April of 1993, there was no reasonable expectation that one could successfully obtain monoclonal antibodies to rapamycins, even in view of the teachings of the prior art, because (a) the general understanding that molecules possessing regions of conformational flexibility (such as the rapamycin macrolide molecules) are less likely to be recognized by B cells, and therefore less likely to generate monoclonal antibodies; (b) the generation of monoclonal antibodies to potent immunosuppressive agents (such as rapamycins) was known to be difficult and unpredictable; (c) although monoclonal antibodies had been generated (with some difficulty) to the prior art compound FK-506, there are substantial structural differences between

rapamycins and FK-506, and rapamycins exhibit significantly different biological activities to FK-506 both at the cellular and the molecular level; (d) no monoclonal antibodies had been generated to an immunosuppressant that has the same mode of action as rapamycins at the cellular level, i.e., (i) blocks the proliferative response of T cells to the IL-2 signal and the T helper effect on B cells, and (ii) suppresses B cell activation and antibody production; and (e) no monoclonal antibodies had been generated to an immunosuppressant that have the same mode of action as rapamycins at the molecular level, i.e., bind to FKBP and then to a target, later identified as mTOR/FRAP/RAFT1.

Moreover, the present specification clearly teaches that antibodies to rapamycins can be obtained using a conjugate other than one at positions 31 and 42, i.e., the specification teaches that conjugates at the position 27 can be used to obtain the rapamycin-specific monoclonal antibodies (see page 8, lines 5 *et seq* and page 12, lines 19 *et seq* of the present specification).

Moreover, the Sedrani references cited by the Examiner in the PTO-Form 892 attached to the Office Action, show that antibodies to rapamycins can be obtained using conjugates other than those describe in the present application.

As noted above, the Examiner has failed to cite any legal precedent in support of her position. However, Applicants cite *Amgen* v. *Hoechst Marion Roussel, Inc.*, 65 USPQ2d 1385 (Fed. Cir. 2003) which clearly holds that the specification merely

needs to teach one method of making the antibody to enable a claim directed to the antibody:

> For a product claim, the application need only enable one method of making the same. An application need not disclose or enable an unclaimed method of making the claimed product.
>
> Where the method is immaterial to the claim, the specification need not describe technological developments concerning the method by which a patented compound is made that may arise after the patent application is filed to meet the enablement requirement. The specification's failure to disclose the later-developed technology cannot invalidate the patent. (Emphasis added)

The Examiner notes Applicants' reliance upon U.S. Patent 5,474,771, issued to Lederman et al for the position that the claims of the present invention need not be limited to use of specific immunogens. However, the Examiner contends that Applicants argument is misplaced because in the present invention there is a basic question of whether or not one skilled in the art would be expected to be able to produce antibodies to rapamycin, whereas there was no such question regarding the protein epitope of Lederman et al, i.e., one skilled in the art would expect that antibodies could be produced to the Claim 1 antigen of Lederman.

The Examiner is requested to note that Lederman Patent contains claims similar to Claim 41. In particular, Claim 1 of the Lederman Patent is as follows:

> Claim 1. A monoclonal antibody which specifically binds and forms a complex with the 5c8 antigen located on the surface of activated

> T cells and thereby inhibits T cell activation of B cells, the 5c8 antigen being an antigen to which monoclonal antibody 5c8 (ATCC Accession No. HB 10916) specifically binds.

Lederman discloses that the deposited 5c8 antibody was obtained using D1.1 cells as the immunogen (see col. 15, lines 18 *et seq*). However, it should be noted that Claim 1 of the Lederman Patent is not limited in terms of the immunogen used to obtain the deposited 5c8 antibody. Thus, by analogy, Claim 41 of the present application also need not be limited in terms of the immunogen used to obtain the claimed monoclonal antibody, contrary to the Examiner's contention.

Indeed, in Lederman, the 5c8 antigen was itself novel *per se*. Thus, prior to the Lederman disclosure, there was no reasonable expectation that one could successfully obtain antibodies to the 5c8 antigen therein, contrary to the Examiner's contention in the outstanding Office Action. Hence, the allowance of Lederman Claim 1 is clearly relevant to, and indicative of, the allowability of present Claims 41 and 47.

Accordingly, Applicants respectfully submit that Claims 41 and 47 are enabled by the present application, and thus request withdrawal of the Examiner's rejection.

In paragraph 5, on page 3 of the Office Action, the Examiner rejects Claim 47 under 35 U.S.C. § 112, second paragraph.

Specifically, the Examiner contends that in view of the expression "obtainable", the claim is unclear since it is not limited to an antibody which is produced using the recited immunogen.

The Examiner notes that this rejection can be overcome by substituting the term "obtainable" with "obtained using".

Accordingly Applicants hereby amend Claim 47 as suggested by the Examiner, thereby rendering moot the Examiner's rejection.

Again, Applicants note that, in paragraph 6, on page 3 of the Office Action, the Examiner indicates that Claims 33-40 and 42-46 have been allowed.

In view of the amendments to Claim 47 and arguments set forth above, reexamination, reconsideration and allowance are respectfully requested.

The Examiner is invited to contact the undersigned at his Washington telephone number on any questions which might arise.

Respectfully submitted,

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Date: June 13, 2003